Epidemiology and Clinical Features of *Cryptosporidium* Infection in Immunocompromised Patients

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INTRODUCTION

Although *Cryptosporidium* was initially described in mice in 1907, it was not until 1976 that it was first reported in association with diarrheal disease in humans, one case in an otherwise healthy child and one in an immunosuppressed adult (33, 40, 83, 84, 95). In otherwise healthy individuals, *Cryptosporidium* spp. typically cause watery or mucoid diarrhea with abdominal pain that can last several days and occasionally several weeks. Spontaneous recovery is the rule, and there is no effective specific therapeutic agent. The infection is spread in a number of ways: from person to person, from animals, via food, and by water. Cryptosporidiosis is now the most common cause of waterborne disease in the United Kingdom and has been associated with drinking water and swimming pool contact (58). Although not quite the commonest cause of waterborne outbreaks in the United States, cryptosporidiosis is responsible for one of the largest waterborne outbreaks ever described (73).

As discussed below, *Cryptosporidium* causes far more serious disease in certain immunosuppressed individuals. The link between *cryptosporidium* infection and drinking water has led authorities in both the United Kingdom and United States to issue advice to immunocompromised people to boil their drinking water under certain circumstances (20a, 34). The United Kingdom guidelines published in 1998 stated that "all water, from whatever source, that might be consumed by immune-compromised persons should be brought to the boil and allowed to cool before use." Unfortunately, the authors did not define what was meant by the phrase "immune-compromised persons." Subsequent advice specified that this meant patients whose T-cell function was compromised and included patients who are immunosuppressed because of human immunodeficiency virus (HIV) infection, children with severe combined immunodeficiency syndrome, and people with CD40 ligand deficiency, also known as hyper-immunoglobulin M syndrome (8). The U.S. advice is not as prescriptive as the British advice but does suggest that patients with HIV infection may wish to boil water for 1 min or use an appropriate filter (20a). Since *Cryptosporidium* oocysts are inactivated within a few seconds at 62°C, it is unclear why water should be boiled for a full minute (54). This is particularly an issue when one considers the difficulty of keeping many of the modern automatic kettles boiling for a full minute. The risk of scalding to those keeping the kettle switch depressed for the full minute is not in our view justified because safety is not increased. The U.S. authorities have also issued similar advice to patients who have undergone a bone marrow transplant (20) although British authorities have elected not to give this advice.

Despite the relative consensus of opinion regarding the seriousness of *Cryptosporidium* infection in patients with AIDS and the importance of protecting these patients from infection, there does not seem to be a shared understanding of the risks to other groups of immunosuppressed patients. This paper will examine the impact of cryptosporidiosis in patients with various immunosuppressive conditions so that guidance on which groups need to take steps to reduce the risk of illness can be better defined.

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IMMUNE RESPONSE TO CRYPTOSPORIDIOSIS

The host immune response to *Cryptosporidium parvum* infection is still poorly understood but has recently been reviewed (79, 117). Many laboratory animals exhibit innate resistance to infection, and much experimental work has tried to determine the specific immune factors responsible for this resistance. The response that normally clears an established infection in a susceptible host probably involves similar mechanisms, but specific immune response mechanisms are probably also important. There is a general consensus that the mechanisms responsible for clearing cryptosporidium from the gastrointestinal tract involve a role for gamma interferon, although the mechanism by which this cytokine imparts resistance is unclear. It is also clear that CD4 T lymphocytes are necessary for the resolution of both acute and chronic cryptosporidiosis. Experimental-infection studies with mice and calves show that immunity is dependent on the number of CD4 T cells increasing within the intestinal intraepithelial lymphocytes and generating gamma interferon Interleukin-12 may play a role, possibly through its ability to induce gamma interferon production (123). Antigen-driven interleukin-12 production in macrophages requires interaction between CD40 on antigen-presenting cells and CD40 ligand on $CD4^+$ T lymphocytes. No difference was found between cryptosporidiosis in normal and B-cell-depleted neonatal mice, suggesting that antibody production may play a less important role in recovery from infection (115). The role of CD8 T cells is unclear, but they appear to play a role in controlling infection in mice (117). Mast cells may play a role in innate resistance in mice (117). Interleukin-2, tumor necrosis factor alpha, and $\gamma\delta^+$ T cells are probably not involved in innate resistance to *C. parvum*, and the role of natural killer (NK) cells remains unclear (117). The potential importance of gamma interferon has recently been highlighted in several studies. Theodos et al. developed a nonhealing mouse model of infection with a targeted disruption of the gamma interferon (118). These mice developed an overwhelming infection of the entire gastrointestinal tract and usually died within 2 to 3 weeks; in contrast, healing mice were free of infection by day 30. Mead and You also demonstrated significant differences in survival between mouse strains with and without the ability to produce gamma interferon (82). In a more recent study in mice with severe combined immunodeficiency (SCID mice), the authors showed that SCID mice remained infected with *Cryptosporidium* spp. for a long time without ill effect but that those with an inability to produce gamma interferon died rapidly (57). They suggested that gamma interferon might be important in immunity against secondary infections, and other evidence suggests that it plays a role in innate immunity.

In a study of human volunteers, jejunal biopsy specimens were examined for gamma interferon mRNA (129). Gamma interferon m-RNA was not detected prior to challenge with *Cryptosporidium* spp. but was detected in samples from 13 of 26 people after deliberate infection. After infection, the gamma interferon mRNA was more commonly found in volunteers with preexisting antibody and in those who did not shed oocysts in the feces. It was suggested that gamma interferon played a more important role in the secondary rather than the primary infections.

CRYPTOSPORIDIOSIS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Epidemiology

A number of studies have investigated the prevalence and epidemiology of cryptosporidiosis in patients with HIV infection. The results of the studies investigating the prevalence of cryptosporidiosis in HIV-positive patients with diarrhea have presented estimates that differ quite markedly from one another, ranging from 0 to 100% with a median of 32% (2, 4, 5, 10, 11, 14, 31, 39, 41, 53, 65, 71, 78, 85, 90, 108, 121, 124). It is not clear how much these differences may be explained by differences in study design, geographical location, population group, sensitivity of laboratory methods, or stage of disease. Nevertheless, it would appear that the prevalence of carriage *Cryptosporidium* spp. oocysts in the absence of diarrhea is very low (5). There have been rather fewer studies that have attempted to define an overall prevalence in HIV-positive individuals, irrespective of whether they have diarrhea. In Europe, cryptosporidiosis seems to affect about 6.6% of HIV-positive individuals (98). A slightly earlier U.S. study in Los Angeles found an overall rate of 3.8% of individuals to be positive during the study period (112).

The risk of infection increases in more profoundly immunosuppressed persons, as measured by the $CD4^+$ T-lymphocyte counts (93, 111). Various social and behavioral factors also increase the risk of infection. For example, in a large multicenter European study the risk of cryptosporidiosis was significantly lower for intravenous drug users than for homosexual men (relative risk, 0.34; 95% confidence interval, 0.22 to 0.54) and for women than for men (relative risk, 0.43; 95% confidence interval, 0.21 to 0.87), suggesting that sexual behavior may be an important risk factor (98). The importance of sexual behavior as a risk factor was also identified in a large U.S. study, where the prevalence of cryptosporidiosis was higher in persons whose suspected HIV exposure category was through sexual contact (3.9%) than among persons in other HIV exposure categories (2.6%; $P < 0.01$) and in immigrants from Mexico (5.2%) than in American-born patients (3.8%; $P < 0.01$). Blacks (2.7%) were less likely than whites (4.1%) and Latinos (4.2%) to be reported with cryptosporidiosis ($P < 0.001$) (112). In another study, HIV-positive patients who owned dogs (but not other pets) also seem to be at increased risk of infection (odds ratio, 2.19; 95% confidence interval, 0.9 to 5.3; $P = 0.05$) (49).

Caputo et al. undertook a cross-sectional serological survey of HIV-positive individuals to look for anti-cryposporidial antibodies (19). They reported that an increased serological response to one or more antigens was related to a number of sexual practices such as having had sex within the past 2 years, having multiple partners during that time, having anal sex, and attending a spa or sauna.

Nosocomial outbreaks of cryptosporidiosis have also been described. For example, an outbreak in a hospital in Copenhagen affected some 18 HIV-positive patients (102). The source of the outbreak was identified as ice from an ice machine in the ward, contaminated by an incontinent psychotic patient with cryptosporidiosis who was using his hands to pick out ice for cold drinks. More recently, Bruce et al. conducted a retrospective cohort study of transmission between room-

mates in a hospital setting (15). They were able to identify 37 HIV-positive patients who had shared a hospital room with 21 *Cryptosporidium*-positive index patients and matched them to other HIV-positive individuals with a similar CD4 count but who had not shared a room with a *Cryptosporidium*-positive patient. None of the 37 exposed individuals became infected, and one of the unexposed controls became infected, suggesting that person-to-person transmission may not be common. However, extrapolation of this experience to other health care settings with different infection control practices may be difficult.

Molecular epidemiology of *Cryptosporidium* isolates has proved useful in determining sources of infection (81). There have been too few studies on the prevalence of different genotypes of *Cryptosporidium* in HIV-infected patients to date to draw firm conclusions. One American study characterized 13 strains from people with AIDS and found that 10 were *C. parvum* type 1 (the human type) and 3 were *C. parvum* type 2 (the calf type) (130). A subsequent American study found that 5 of 10 AIDS patients were infected by *C. parvum* genotype 1 and 1 was infected by *C. parvum* genotype 2 and the remaining isolates were other species (see below) (101). A study of *Cryptosporidium* isolates from HIV-infected patients from Kenya, Switzerland, and the United States found that of 22 isolates examined, 6 were genotype 1, 8 were genotype 2, and 8 were non-*parvum* strains, including *C. meliagridis* (89). The genotypes commonly found in humans are *C. parvum* genotypes 1 (the human strain) and 2 (the calf strain), although *C. meliagridis* and an as yet unnamed dog strain have been described (100, 131). Although *C. parvum* genotype 1 strains seem to predominate in AIDS patients in North America, it is unclear whether this represents increased person-to-person transmission.

In addition to being at increased risk of infection by *C. parvum*, patients with AIDS have been reported to be infected with other *Cryptosporidium* spp. Xiao et al. found nine non-*parvum* species of *Cryptosporidium*: *C. wrairi*, *C. meleagridis*, *C. saurophilum*, *C. felis*, *C. baileyi*, *C. muris*, *C. andersoni*, *C. serpentis*, and *C. nasorum* (131). In the American study mentioned above, 3 of 10 isolates from AIDS patients were *C. felis* and 1 was an unnamed *Cryptosporidium* sp. similar to one previously isolated from a dog (101). In the study from Kenya, Switzerland, and the United States, it was found that of 22 isolates examined 6 were *C. felis* and 2 were *C. meleagridis* (89). Ditrich et al. reported an infection in a patient which they identified as due to *C. baileyi*, normally a parasite of birds (35). However, this organism was later shown to be antigenically different from *C. baileyi* (36). Recent work in the United Kingdom showed that the feces from six HIV-positive individuals yielded *C. parvum* (two patients), *C. felis* (two patients), and *C. meleagridis* (two patients) (99; J. McLauchlin, personal communication). In 23 other immunosuppressed patients, of whom 7 were CD40 ligand deficient, 19 had *C. parvum* and 4 had *C. meleagridis*; of these, 8 had a mixture of genotypes (McLauchlin, personal communication). While isolates of non-*parvum* species from humans may be genetically very similar to isolates from animals and birds, there is limited evidence of cross-infectivity (100). Although it was originally thought that non-*parvum* species were restricted to AIDS patients, recent evidence has shown that these species can also infect immunocompetent individuals (22, 99, 100, 132).

From the discussion above, it is clear that HIV-positive patients, particularly those with AIDS (as measured by a low CD4 count), are at increased risk of being infected with cryptosporidiosis. This risk is increased when individuals engage in high-risk sexual behavior. The high prevalence of *Cryptosporidium* spp. in AIDS patients is probably related to an increased risk of acquiring infection from infected contacts and prolonged excretion, which in turn increases the risk of subsequent transmission. AIDS patients also seem to be more commonly infected with *Cryptosporidium* spp. other than *C. parvum* than do immunocompetent individuals. In the four studies on isolates from AIDS patients discussed above, a total of 51 isolates were identified of which 14 were non-*parvum* (27.5%; 95% confidence interval, 15.9 to 41.7%), considerably higher than found in typing isolates from the general population (89, 99, 101, 130). This suggests that different risk factors and transmission routes may be involved in non-*C. parvum* infections relative to *C. parvum*. Immunodeficiency may also alter the host susceptibility to *Cryptosporidium* species that are not normally infectious to humans.

Clinical Features

Blanshard et al. described the various presentations of cryptosporidiosis in HIV-positive patients in London (13). In this population, cryptosporidiosis was diagnosed in some 5% of all patients with HIV infection and 21% of patients with AIDS. The authors studied the course of infection in 128 patients. Transient infections were found in 28.7% and were more common in the less strongly immunosuppressed patients. Fulminant disease, the passage of more than 2 liters of stool/day, affected 7.8% of patients but only those with a CD4 count less than $50/\text{mm}^3$. Chronic disease was present in 59.7% of patients, and 3.9% of infections were asymptomatic. Patients with fulminant disease survived for a median of only 5 weeks, compared with 20 weeks for those with chronic diarrhea and 36 weeks for those with transient infection.

A second study from London investigated the outcome in 38 HIV-positive patients with cryptosporidiosis (80). Of these 38 patients, only 11 (29%) experienced a clinical remission. Remission had a major impact on survival. The patients who experienced remission had a median survival time of 66 weeks compared to only 11.5 weeks for the nonremission group ($P = 0.001$). The median lymphocyte count of the remission group was significantly higher than that of the nonremission group ($1,100 \times 10^6$ and 550×10^6/liter, respectively; $P = 0.003$).

A few years later, U.S. workers also described four clinical syndromes, similar to but slightly different from those found by the British group: chronic diarrhea (affecting 36% of patients), cholera-like disease (33%), transient diarrhea (15%), and relapsing illness (15%) (75). Infected patients had a significantly shorter duration of survival from the time of diagnosis than did *Cryptosporidium*-negative AIDS patients (240 and 666 days, respectively; $P = 0.0004$). Survival was independent of sex, race, or injection drug use. Interestingly, antiretroviral use was protective against disease (odds ratios, 0.072; $P = 0.0001$).

Italian workers investigated the particular outcome of *Cryptosporidium* infection in children with HIV infection (53). A

total of 35 children were examined every 2 months and, if found to have diarrhea were tested for *Cryptosporidium*; 5 (14%) were positive, 4 of whom recovered spontaneously. All five positive patients had AIDS. Diarrhea in those found to be *Cryptosporidium* positive was much more protracted than in those with diarrhea due to other causes.

One study has shown that prognosis is independently related to two factors measured at the time of *Cryptosporidium* diagnosis: CD4 count of $\leq$53 cells/mm^3 versus >53 cells/mm^3 (relative hazard, 6.18; 95% CI, 2.99 to 12.76) and hematocrit of $\leq$37% versus >37% (relative hazard, 2.27; 95% CI, 1.22 to 4.22) (29). The median survival in the subgroup with a CD4 count of >53 and hematocrit of >37% was 1,119 days compared to only 204 days in the subgroup with a CD4 count of <53 and hematocrit of <37%. This study also showed that an initial AIDS-defining diagnosis of cryptosporidiosis was a poor prognostic factor compared to other possible diagnoses (relative hazard of death, 2.01; 95% CI, 1.38 to 2.93).

One aspect of chronic cryptosporidiosis in patients with AIDS is the large weight loss that many experience. One study from France reported that the severity of weight loss in such patients is independently associated with levels of nutrient intake ($P < 0.005$) and high stool frequency ($P < 0.01$) but not with nutrient malabsorption (12).

As well as developing a more severe form of typical gastrointestinal disease, people with HIV infection can develop atypical disease presentations, affecting body systems not usually affected in immunocompetent individuals. Some of these unusual presentations are discussed below.

Atypical gastrointestinal disease. In a review of the literature published in 1997, the authors were able to identify only 16 cases of gastric cryptosporidiosis (127). Despite this, gastric involvement is probably more common than was previously realized, but detection is difficult because diagnosis requires upper gastrointestinal tract endoscopy. In an endoscopic study of 71 patients with AIDS and chronic diarrheal illness or other gastrointestinal disorders of unexplained origin, 24 individuals were positive for cryptosporidiosis. Of these 24 patients, 16 (67%) had parasites in the gastric epithelium (104). Few of the patients reported any symptoms that could be correlated with this gastritis, and the authors concluded that there was no clear correlation between gastric colonization and related clinical and pathological features. One particularly problematic complication of gastric involvement is antral narrowing and gastric outlet obstruction (21, 45, 59, 91). Such gastric outlet obstruction can lead to nausea and vomiting and eventually may cause a severe reduction in nutrient intake.

A further unusual complication of cryptosporidiosis in AIDS patients is pneumatosis cystoides intestinalis (30, 106, 109). Pneumatosis cystoides intestinalis is characterized by the presence of thin-walled, gas-containing cysts in the intestinal wall. Sometimes these cysts can rupture, resulting in a pneumoretroperitoneum and pneumomediastinum.

There is a case report of cryptosporidiosis affecting the esophagus in a 2-year-old child and resulting in vomiting and dysphagia (64). Finally, there is also a case report of *Cryptosporidium* infection causing appendicitis (96). The diagnosis was confirmed histologically after an appendectomy was performed.

Biliary tract disease. Cholangitis, and particularly sclerosing cholangitis, is an important complication of AIDS. Although not appearing to adversely affect survival, the disease can be a cause of significant pain (43). Of 20 patients suffering from cholangitis in a British study, 13 had cryptosporidiosis. In a Spanish study of 43 AIDS patients with chronic diarrhea due to *Cryptosporidium* infection, 8 patients (18.6%) were reported to have *Cryptosporidium* infection of the common bile duct (71).

Following the waterborne outbreak of cryptosporidiosis in Milwaukee, Vakil et al. reported that of 82 patients, believed to have become infected at the time of the outbreak, 24 (29.3%) reported biliary symptoms (126). The presence of biliary symptoms was a strong indicator of the prognosis since 83% of patients with symptoms died within the following year compared to only 48% of those without. In our view, it is doubtful that this difference was due directly to the biliary involvement but is more likely to reflect the point that more severely immunocompromised persons are more likely to experience biliary involvement.

Pancreatitis. A series of 15 autopsies on patients with AIDS and cryptosporidiosis showed that five had evidence of infection of the pancreas (50). Histological changes were generally mild and were limited to hyperplastic squamous metaplasia. Three people with AIDS presented with acute or chronic pancreatitis related to cryptosporidiosis (17). All three patients had abdominal pain resistant to analgesics, increased serum amylase levels, and abnormalities at both sonography and computed tomography. Endoscopic retrograde cholangiopancreotography revealed papillary stenosis in all three patients. It is difficult to assess the impact of cryptosporidiosis-related pancreatic disease. Certainly, the first study does not suggest significant morbidity due to *Cryptosporidium* in the pancreas.

Respiratory tract disease. In the study from Spain mentioned above, 7 of 43 patients (16.3%) with chronic diarrhea due to *Cryptosporidium* had *Cryptosporidium* oocysts detectable in the sputum (71). Of these seven patients, five had respiratory symptoms and an abnormal chest radiograph; *Mycobacterium tuberculosis* was isolated in two of the five, and *M. avium* was isolated in another two. The remaining two patients had no respiratory symptoms and normal chest radiographs. An additional case series of five patients with respiratory cryptosporidiosis, all of whom had respiratory symptoms, was reported from Spain (27). Again, another respiratory pathogen was isolated in four patients (*M. tuberculosis* in two, *M. fortuitum* one, cytomegalovirus and *Pneumocystis carinii* in one). This latter group also reviewed literature published to that point and were able to identify some 57 patients with respiratory cryptosporidiosis, 40 of whom had another pathogen detected. Given the difficulty in diagnosing many respiratory pathogens, it is not clear to us how relevant respiratory disease secondary to cryptosporidiosis is in the prognosis of and symptoms associated with AIDS. Neither of the papers discussed above can be taken to show that cryptosporidiosis causes respiratory disease.

Dunand et al. reported on 5 of their own cases and reviewed 14 other cases of parasitic sinusitis in HIV-positive patients from the literature (37). Symptoms often included fever and chills in addition to local tenderness and discharge. Although the prognosis was frequently poor, this was due to other complications of HIV infection.

Therapy

There have been a large number of studies aimed at developing a satisfactory therapy for cryptosporidiosis, particularly in patients with AIDS. Although several agents have been found to have some activity (most notably macrolides such as spiramycin and clarithromycin, the aminoglycoside paromomycin, and ionophores such as Lasalocid and maduramycin), results have been mixed (52, 55, 122). In part because of the failure of other therapeutic approaches, there have been several attempts at passive antibody-based immunotherapy for cryptosporidial infections (32). These have also had limited success. One therapeutic intervention that has a dramatic effect on cryptosporidiosis in AIDS patients is antiretroviral therapy leading to recovery of the CD4 count. In one study of two patients with cryptosporidiosis, both were free from the parasite within 24 weeks after starting antiretroviral therapy (44). This finding was confirmed in another, larger study, where all patients taken antiretroviral agents showed clinical recovery (74). Two patients subsequently relapsed after the therapy, was stopped. The authors noted that resolution of the diarrhea seemed to be related to an increased $CD4^+$ cell count rather than to the viral load. Furthermore, at least one clinic has noted a decrease in problems related to cryptosporidiosis in their AIDS patients since the onset of the widespread use of protease inhibitors (68); and eradication of infection in people on highly active antiretroviral therapy has also been observed (87). These findings give further support to the observation that it is cellular immunity that is of paramount importance in clearing *Cryptosporidium* infection.

CRYPTOSPORIDIOSIS IN OTHER IMMUNOSUPPRESSED INDIVIDUALS

Primary Immunodeficiency Diseases

The primary immunodeficiencies are uncommon or rare inherited defects in one or more aspects of the body's immune mechanisms. These diseases and their genetic causes have been reviewed elsewhere (6, 110). Many different primary immunodeficiency diseases have been described, although most can be classified into one of a few categories: the combined immunodeficiencies, which affect both T and B lymphocytes; the predominantly antibody deficiencies; the complement deficiencies; and the defects in phagocyte number and function.

There are far fewer case reports or other investigations of cryptosporidiosis in these patients compared to those of HIV-related disease. However, this may simply reflect the much smaller number of cases available for study. Indeed, most of what we can infer about the clinical progression of cryptosporidiosis in these patients comes from a few case reports. Because of this, we can infer hazard but cannot really develop a clear understanding of risk and the likely prognosis of disease.

Probably the most serious immunodeficiency, from the point of cryptosporidiosis risk, is severe combined immunodeficiency syndrome. Kocoshis et al. described small intestinal and pulmonary cryptosporidiosis in an infant with severe combined immunodeficiency (67). The patient died in the fifth month of his illness despite receiving parenteral alimentation and undergoing thymus transplantation. His clinical course was similar to that of other patients with fatal immunodeficiencies and cryp-

tosporidiosis. In addition, extraintestinal sites were affected. Autopsy demonstrated *Cryptosporidium* affecting the epithelium of the small intestine, pancreatic duct, and bronchioles.

Protracted cryptosporidiosis was also reported in a patient with selective immunoglobulin A, and *Saccharomyces* opsonin deficiencies (60).

X-linked hyper-immunoglobulin M syndrome, once considered a clinical variant of hypogammaglobulinemia, is a severe immunodeficiency with significant T-cell impairment and mutations in the CD40 ligand gene. The disease has a high mortality rate, and the clinical and immunologic features of 56 patients with this condition have been presented (56, 69). Chronic diarrhea and liver involvement (both often associated with *Cryptosporidium* infection) were common.

Gomez Morales et al. reported a protracted infection in a child who had become unwell in the second week of life, with chronic intractable diarrhea and significant weight loss (51). Initial immunological assessment excluded HIV or primary immunodeficiency syndrome. However, further analyses suggested gamma interferon deficiency.

Cryptosporidiosis in Patients with Malignant Disease

There have been several studies investigating the epidemiology and prognosis of *Cryptosporidium* infection in patients with malignant disease. For example, Tanyuksel et al. reported on a study, done in Turkey, of 106 fecal samples from patients with diarrhea and various cancers (116). *Cryptosporidium* oocysts were detected in 18 (17.0%), of these 106 patients. The authors found no oocysts in samples from 60 cancer patients without diarrhea. A similar study of 560 patients with cancer and diarrhea in India found oocysts in 7 patients (1.3%) (113). Of these seven patients, five had hematological cancers.

Two studies have investigated the prevalence of *Cryptosporidium* in children with cancer. The first, from New South Wales, investigated 149 stool samples from 60 children with cancer and diarrhea and found none to be positive (16). By comparison, 13% of stools from non-oncology patients were positive. The second study was performed in Malaysia, where *Cryptosporidium* was found in 2% of children (86).

Three of the four studies mentioned above were in tropical countries, and their relevance to the industrialized western nations is unclear. Nevertheless, the evidence would appear to indicate that *Cryptosporidium* does not pose a particularly special risk to cancer patients generally. The exception to the rule seems to be leukemia and other hematological malignancies.

Cryptosporidiosis does seem to cause unusually severe infection in children with leukemia. Stine et al. described severe diarrhea in a child with acute lymphocytic leukemia, although the child recovered (114). Lewis et al. described a relapsing course of infection in a child with acute lymphoblastic leukemia (70). One small series of six cases in children with acute leukemia or lymphoma showed that two patients died with evidence of persistent infection (42); the remaining four recovered after chemotherapy regimens were modified.

A paper from Italy reported the progress of 20 patients with cryptosporidiosis, all of whom also had a hematological malignancy and were receiving chemotherapy and some of whom had also undergone bone marrow transplantation (47). Most of the patients were adults. Of these patients, 5 had severe diar-

rhea, 10 had moderate diarrhea, and 5 were asymptomatic carriers of *Cryptosporidium* spp. Extraintestinal cryptosporidiosis with pulmonary involvement was observed in one patient who subsequently died from intractable cryptosporidiosis and *Candida* infection. The remaining patients recovered, although four relapsed. Asymptomatic carriage of *Cryptosporidium* has been reported in two patients with leukemia (46). Respiratory involvement has also been described by others (119, 128).

The recent years have seen a dramatic increase in the use of bone marrow transplantation to treat leukemia and other hematological malignancies. In the series of 20 patients described above, 11 had undergone an allogeneic or autologous bone marrow transplantation (47). In general, there was no difference in severity between those that had or had not received such transplantation for their underlying disease. Nevertheless, there has been some interest in the risk of cryptosporidiosis in patients during or after bone marrow transplantation. In addition to that described above, there have been several reports in the literature of particularly severe diarrhea in patients during or after bone marrow transplantation. Gentile et al. described two such patients with profuse diarrhea (47), as did Manivel et al. (76) Pulmonary cryptosporidiosis has also been described (66, 92). Two of the three patients described in these two papers died as a result of their infection; the third patient survived after intensive therapy. There has been a description of one outbreak of cryptosporidiosis in a bone marrow transplantation unit (77).

Cryptosporidiosis in Patients following Solid-Organ Transplantation

Cryptosporidiosis has been found in children after liver transplantation (18, 48, 125). In a study from Belgium of 461 children following liver transplantation, 3 developed diffuse cholangitis associated with intestinal *Cryptosporidium* carriage (18). All three required reoperation on the bile duct anastomosis, but biliary cirrhosis developed in one patient, requiring retransplantation. In a retrospective study from Pittsburgh, four cases of cryptosporidiosis were identified in some 1,160 nonrenal, abdominal organ transplant recipients, all children (48). Three of these four occurred in patients receiving liver transplants, and one occurred following a small bowel transplantation. All four patients spontaneously resolved their infections.

Cryptosporidiosis has been described in renal transplant patients by several authors, although the disease does not appear to be unusually severe or involve extraintestinal sites (28, 103). A Brazilian study compared the frequency of infection by *C. parvum* in two groups of renal transplant recipients on immunosuppressive therapy. One group consisted of 23 individuals with renal transplants, and the other consisted of 32 patients with chronic renal insufficiency, who periodically underwent hemodialysis. A third group of 27 patients with systemic arterial hypertension, not immunosuppressed, was used as a control. The results showed frequencies of *C. parvum* infection of 34.8, 25, and 17.4% for the transplant recipients, the patients undergoing hemodialysis, and the control group, respectively. Statistical analysis showed no significant differences among the three groups (26). Contrary to this view was a study from Turkey which examined 115 fecal specimens from 69 renal

transplant recipients and 42 fecal specimens from 42 control patients (97). Of the 69 transplant recipients, 13 (18.8%) had *Cryptosporidium* spp. in at least one fecal specimen, and the rate was significantly higher in the renal transplant recipients than in the control group ($P < 0.05$), although multiple samples were taken from the renal transplant group and not the other. The authors used antiparasitic drugs in 16 symptomatic patients, all of whom improved, although whether this was as a result of therapy is not clear.

Malnutrition

Cryptosporidiosis is more common and more severe in malnourished children. One early study from the West Indies reported on the investigation of 513 stool samples, of which 77 were from malnourished children (72). *Cryptosporidium* was detected in 25 (4.9%) of 513 samples and in 15 (19.5%) of the 77 samples from malnourished children. All the malnourished children with cryptosporidiosis were admitted to hospital, where they presented with dehydration (87%), vomiting (93%), fever (100%), and diarrhea (100%) which lasted an average of 15.3 days. Two of these children died. Of the 10 cases of cryptosporidiosis in well-nourished children, only 20% of the children presented with dehydration, 40% presented with vomiting, and 50% presented with fever. Diarrhea was also less prolonged, and only four patients were admitted to hospital; all survived.

Many groups have also reported the higher prevalence of cryptosporidiosis in malnourished children. In a study from Israel, *Cryptosporidium* was detected in 30 (13.5%) of 221 children admitted to hospital with diarrhea (105). In 77 outpatients with diarrhea, *Cryptosporidium* was detected only in 4 (5.2%). Outpatients were better nourished than inpatients. Children with *Cryptosporidium*-positive stools were significantly more malnourished than children in whom *Cryptosporidium* was not detected. Neira et al. reported a study of cryptosporidiosis in malnourished children (94). The prevalence in the children at the Nutritional Recovery Center (the most severely malnourished individuals) was 8.5%, and the prevalence at an ambulatory undernourished center (less severely malnourished children) was only 1.9%. A case-control study of Peruvian children admitted to hospital with diarrhea sought to determine the clinical differences between children with and without cryptosporidium (107). There were 24 case-control pairs. The only significant difference was that children with cryptosporidiosis were significantly more likely to be malnourished. It was also noted that two severely malnourished children with cryptosporidiosis died. In a study from India, *Cryptosporidium* was identified in 13 of 100 children with diarrhea, of whom 6 (46%) were malnourished (61). The same study found *Cryptosporidium* in 7 of 50 children with chronic diarrhea, 6 (86%) of whom were malnourished. In a study in Gabon, the carriage rate in children with malnutrition was 31.8%, almost twice that found in adequately nourished children (16.8%) ($P < 0.01$) (38). A study in Mexico also showed an increased risk of cryptosporidiosis in malnourished children, especially when those children were not being breast-fed (63). In a study of 55 HIV-negative children with acute diarrhea in Tanzania, 7 were positive for *Cryptosporidium* infection, and all 7 were malnourished (20).

However, these studies that show increased carriage of cryptosporidiosis in malnourished children do not distinguish between cause and effect. Given that cryptosporidiosis causes diarrheal disease, the infection may push children into the malnourished state rather than malnourishment being a risk factor for cryptosporidiosis. This hypothesis is supported by a study of a cohort of 1,064 children from Guinea-Bissau (88). Children who developed cryptosporidiosis were no different in weight or height before the infection than were children who did not. However, boys and girls who developed cryptosporidiosis lost 392 and 294 g, respectively, on average, and this weight loss, relative to their peers, was not caught up during the period of the study. Other studies have also demonstrated the long-term impact on subsequent growth of individuals with symptomatic and asymptomatic cryptosporidiosis (3, 24, 25).

A point prevalence survey was done on 205 institutionalized orphans up to 61 months old in Bangkok, Thailand (62). *Cryptosporidium* was identified in 17 children (8%), *Giardia lamblia* was identified in 42 (20%), and 3 children (1%) harbored both parasites. Diarrhea was present in 36% of children with *Cryptosporidium* alone, 10% of those with *G. lamblia* alone, and 20% of those with neither parasite. Chronic nutritional status (height/age) was similar in all groups, but acute nutritional status (weight/height) was lower in children with *Cryptosporidium* infection (Z score = -1.39 ± 0.13 [mean $\pm$ standard error of the mean]) than in children with *G. lamblia* infection (Z score = -0.56 ± 0.26) or neither parasite (Z score = -0.78 ± 0.13; $P = 0.05$).

The study from Bangkok would suggest that cryptosporidiosis is a major factor in the causation of acute malnutrition rather than malnutrition being a risk factor for cryptosporidiosis. However, the results of all the studies are still conflicting on this issue and the relationship between malnutrition and cryptosporidiosis is more complex than it first appears. What is obvious is that *Cryptosporidium* infection has an effect on growth and this is likely to be more severe in children who are already malnourished. Such children also seem to be more at risk of death or prolonged illness.

Diabetes

There are reports of three patients with diabetes suffering chronic diarrhea due to cryptosporidiosis (23, 120). However, given the many people living with diabetes in the world, one would expect to have seen many more reports of severe disease in this group if diabetes patients are at increased risk of severe cryptosporidiosis. Indeed, one study from Egypt reported that of all patient groups examined, the prevalence of cryptosporidiosis was lowest in those with diabetes (1).

CONCLUSIONS

It is now well known that people who are immunosuppressed secondary to HIV infection are at higher risk for *Cryptosporidium* infection and that carriage of the parasite is associated with diarrheal disease in most cases. Furthermore, in those with diarrhea, the disease is much more severe and prolonged than in otherwise healthy individuals. There is good evidence that risk of fecal carriage, severity of illness, and development of unusual complications of cryptosporidiosis are directly related to the CD4 count (13, 29, 74, 93, 111). It would appear

from these studies that patients with CD4 counts of less than 50 are at greatest risk for both severity of disease and prolonged carriage. However, behavioral factors such as sexual activity (most particularly having multiple sexual partners and engaging in anal sex) also play a significant role in the increased prevalence of infection in HIV-infected patients (19, 49, 98). From the cumulative evidence presented in this review, it is clear that advice to patients with AIDS on how to avoid infection, including the potential benefits of avoiding unboiled tap water, contact with young animals, and swimming, is extremely important.

What is not clear is the need for such advice in HIV-positive patients who are not immunosuppressed due to early disease or antiretroviral therapy. There is little evidence that HIV-positive patients with a CD4 count of over 200/mm³ suffer much more severe or prolonged disease than do HIV-negative individuals. The major concern in this group is whether an infection, if acquired when the CD4 count exceeds 200/mm³, will not be cleared and may relapse once the patient becomes immunocompromised. The report of relapse in two patients by Maggi et al. would support this hypothesis (74). However, given the ubiquitous nature of *Cryptosporidium* spp., it is not clear whether these represent relapse or reinfection. However, if it is found that relapse is common in HIV-positive patients once they become immunosuppressed, then all HIV-positive patients should be advised to take precautions. This is an issue that needs to be investigated as a matter of priority. On the available evidence, we would support the need for HIV-positive people with CD4 counts of less than 200/mm³, but not other HIV-positive individuals, to boil their drinking water.

The issue in HIV-negative individuals is even more uncertain. Although there are relatively few studies in patients with primary immunodeficiencies, it would appear that the risk is largely limited to those individuals with impaired T-cell function (56, 67, 69). In malignant disease, the same appears to be true, with the risk of severe disease being limited largely to children with acute leukemia and lymphoma (42, 46, 47, 119, 128). Interestingly, bone marrow transplantation does not seem to confer any additional risk over that of the underlying disease (47). Although there have been a number of papers investigating the impact of cryptosporidiosis following solid-organ transplantation, their conclusions have been somewhat contradictory (18, 28, 48, 103, 125). Whether this is due to differing degrees of immune-suppression is unclear.

The conclusions that can be drawn from all these reports is that cryptosporidiosis is unlikely to be more serious than normal except in individuals with impaired T-cell function equivalent to a CD4 count of less than 50/mm³. This is the case whatever the cause of the impairment, whether it is inherited or due to HIV infection, other disease, or therapy. Such patients should be advised about the need to avoid the risk of cryptosporidiosis as far as possible. If the period of immunosuppression is likely to be short-lived, then rigorous protection may not be indicated, since the illness will resolve as the immune status recovers. From the evidence reviewed in this paper, we would conclude that people with a primary immunodeficiency affecting T cells should take additional precautions, including boiling drinking water, avoiding contact with young pets, and avoiding swallowing water while swimming. Children with acute leukemias should also be similarly advised. How-

ever, we do not consider that there is any real value in advising other people with malignant disease or organ transplant recipients to boil water.

REFERENCES

1. **Abaza, S. M., L. M. Makhlouf, K. A. el-Shewy, and A. A. el-Moamly.** 1995. Intestinal opportunistic parasites among different groups of immunocompromised hosts. J. Egypt. Soc. Parasitol. **25:**713–727.
2. **Agarwal, A., S. Ningthouja, D. Sharma, Y. Mohen, and N. B. Singh.** 1998. *Cryptosporidium* and HIV. J. Indian Med. Assoc. **96:**276–277.
3. **Agnew, D. G., A. A. Lima, R. D. Newman, T. Wuhib, R. D. Moore, R. L. Guerrant, and C. L. Sears.** 1998. Cryptosporidiosis in northeastern Brazilian children: association with increased diarrhea morbidity. J. Infect. Dis. **177:**754–760.
4. **Anand, L., N. G. Brajachand, and C. H. Dhanachand.** 1996. Cryptosporidiosis in HIV infection. J. Commun. Dis. **28:**241–244.
5. **Ananthasubramanian, M., S. Ananthan, R. Vennila, and S. Bhanu.** 1997. *Cryptosporidium* in AIDS patients in south India: a laboratory investigation. J. Commun. Dis. **29:**29–33.
6. **Anonymous.** 1997. Primary immunodeficiency diseases. Report of a WHO scientific group. Clin. Exp. Immunol. **109**(Suppl. 1):1–28.
7. **Reference deleted.**
8. **Anonymous.** 1999. *Cryptosporidium* in water and the immunocompromised. Commun. Dis. Rep. Wkly. **9:**289, 292.
9. **Reference deleted.**
10. **Arikan, S., S. Erguven, Y. Akyon, and A. Gunalp.** 1999. Cryptosporidiosis in immunocompromised patients in a Turkish university hospital. Acta Microbiol. Immunol. Hung. **46:**33–40. s
11. **Ballal, M., T. Prabhu, A. Chandran, and P. G. Shivananda.** 1999. *Cryptosporidium* and *Isospora belli* diarrhea in immunocompromised hosts. Indian J. Cancer **36:**38–42.
12. **Beaugerie, L., F. Carbonnel, F. Carrat, A. A. Rached, C. Maslo, J. P. Gendre, W. Rozenbaum, and J. Cosnes.** 1998. Factors of weight loss in patients with HIV and chronic diarrhea. J. Acquired Immune Defic. Syndr. **19:**34–39.
13. **Blanshard, C., A. M. Jackson, D. C. Shanson, N. Francis, and B. G. Gazzard.** 1992. Cryptosporidiosis in HIV-seropositive patients. Q. J. Med. **85:**813–823.
14. **Brandonisio, O., P. Maggi, M. A. Panaro, L. A. Bramante, A. Di Coste, and G. Angarano.** 1993. Prevalence of cryptosporidiosis in HIV-infected patients with diarrhoeal illness. Eur. J. Epidemiol. **9:**190–194.
15. **Bruce, B. B., M. A. Blass, H. M. Blumberg, J. L. Lennox, C. del Rio, and C. R. Horsburgh, Jr.** 2000. Risk of *Cryptosporidium parvum* transmission between hospital roommates. Clin. Infect. Dis. **31:**947–950.
16. **Burgner, D., N. Pikos, G. Eagles, A. McCarthy, and M. Stevens.** 1999. Epidemiology of *Cryptosporidium parvum* in symptomatic paediatric oncology patients. J. Paediatr. Child Health **35:**300–302.
17. **Calzetti, C., G. Magnani, D. Confalonieri, A. Capelli, S. Moneta, P. Scognamiglio, and F. Fiaccadori.** 1997. Pancreatite da *Cryptosporidium parvum* in pazienti con grave deficit immunitario correlato ad infezione da HIV. Ann. Ital. Med. Int. **12:**63–66.
18. **Campos, M., E. Jouzdani, C. Sempoux, J. P. Buts, R. Reding, J. B. Otte, and E. M. Sokal.** 2000. Sclerosing cholangitis associated to cryptosporidiosis in liver-transplanted children. Eur. J. Pediatr. **159:**113–115.
19. **Caputo, C., A. Forbes, F. Frost, M. I. Sinclair, T. R. Kunde, J. F. Hoy, and C. K. Fairley.** 1999. Determinants of antibodies to *Cryptosporidium* infection among gay and bisexual men with HIV infection. Epidemiol. Infect. **122:**291–297.
20. **Cegielski, J. P., Y. R. Ortega, S. McKee, J. F. Madden, L. Gaido, D. A. Schwartz, K. Manji, A. F. Jorgensen, S. E. Miller, U. P. Pulipaka, A. E. Msengi, D. H. Mwakyusa, C. R. Sterling, and L. B. Reller.** 1999. *Cryptosporidium*, *Enterocytozoon*, and *Cyclospora* infections in pediatric and adult patients with diarrhea in Tanzania. Clin. Infect. Dis. **28:**314–321.
20a.**Centers for Disease Control and Prevention.** 1999. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Morb. Mortal. Wkly. Rep. **48**(RR-10):1–66.
20b.**Centers for Disease Control and Prevention.** 2000. Guidelines for the preventing opportunistic infections among hematopoietic stem cell transplant recipients. Morb. Mortal. Wkly. Rep. **49**(RR-10):1–128.
21. **Cersosimo, E., C. J. Wilkowske, J. E. Rosenblatt, and J. Ludwig.** 1992. Isolated antral narrowing associated with gastrointestinal cryptosporidiosis in acquired immunodeficiency syndrome. Mayo Clinic Proc. **67:**553–556.
22. **Chalmers, R. M., K. Elwin, and A. Thomas.** Unusual types of cryptosporidia are not restricted to immunocompromised patients. J. Infect. Dis., in press.
23. **Chan, A. W., I. A. MacFarlane, and J. M. Rhodes.** 1989. Cryptosporidiosis as a cause of chronic diarrhoea in a patient with insulin-dependent diabetes mellitus. J. Infect. **19:**293.
24. **Checkley, W., L. D. Epstein, R. H. Gilman, R. E. Black, L. Cabrera, and C. R. Sterling.** 1998. Effects of *Cryptosporidium parvum* infection in Peru-

25. **Checkley, W., R. H. Gilman, L. D. Epstein, M. Suarez, J. F. Diaz, L. Cabrera, R. E. Black, and C. R. Sterling.** 1997. Asymptomatic and symptomatic cryptosporidiosis: their acute effect on weight gain in Peruvian children. Am. J. Epidemiol. **145:**156–163.
26. **Chieffi, P. P., Y. A. Sens, M. A. Paschoalotti, L. A. Miorin, H. G. Silva, and P. Jabur.** 1998. Infection by *Cryptosporidium parvum* in renal patients submitted to renal transplant or hemodialysis. Rev. Soc. Bras. Med. Trop. **31:**333–337.
27. **Clavel, A., A. C. Arnal, E. C. Sanchez, J. Cuesta, S. Letona, J. A. Amiguet, F. J. Castillo, M. Varea, and R. Gomez-Lus.** 1996. Respiratory cryptosporidiosis: case series and review of the literature. Infection **24:**341–346.
28. **Clifford, C. P., D. W. Crook, C. P. Conlon, A. P. Fraise, D. G. Day, and T. E. Peto.** 1990. Impact of waterborne outbreak of cryptosporidiosis on AIDS and renal transplant patients. Lancet **335:**1455–1456.
29. **Colford, J. M., Jr., I. B. Tager, A. M. Hirozawa, G. F. Lemp, T. Aragon, and C. Petersen.** 1996. Cryptosporidiosis among patients infected with human immunodeficiency virus. Factors related to symptomatic infection and survival. Am. J. Epidemiol. **144:**807–816.
30. **Collins, C. D., C. Blanshard, M. Cramp, B. Gazzard, and J. A. Gleeson.** 1992. Case report: pneumatosis intestinalis occurring in association with cryptosporidiosis and HIV infection. Clin. Radiol. **46:**410–411.
31. **Cotte, L., M. Rabodonirina, M. A. Piens, M. Perreard, M. Mojon, and C. Trepo.** 1993. Prevalence of intestinal protozoans in French patients infected with HIV. J. Acquired Immune Defic. Syndr. **6:**1024–1029.
32. **Crabb, J. H.** 1998. Antibody-based immunotherapy of cryptosporidiosis. Adv. Parasitol. **40:**121–49.
33. **Crawford, F. G., and S. H. Vermund.** 1988. Human cryptosporidiosis. Crit. Rev. Microbiol. **16:**113–159.
34. **Department of the Environment, Transport and the Regions, and Department of Health.** 1998. *Cryptosporidium* in water supplies. Third Report of the Group of Experts. HMSO, London, United Kingdom.
35. **Ditrich, O., L. Palkovic, J. Sterba, J. Prokopic, J. Loudova, and M. Giboda.** 1991. The first finding of *Cryptosporidium baileyi* in man. Parasitol. Res. **77:**44–47.
36. **Ditrich, O., P. Kopacek, and Z. Kucerova.** 1993 Antigenic characterization of human isolates of cryptosporidia. Folia Parasitol. **40:**301–305.
37. **Dunand, V. A., S. M. Hammer, R. Rossi, M. Poulin, M. A. Albrecht, J. P. Doweiko, P. C. DeGirolami, E. Coakley, E. Piessens, and C. A. Wanke.** 1997. Parasitic sinusitis and otitis in patients infected with human immunodeficiency virus: report of five cases and review. Clin. Infect. Dis. **25:**267–272.
38. **Duong, T. H., D. Dufillot, J. Koko, R. Nze-Eyo'o, V. Thuilliez, D. Richard-Lenoble, and M. Kombila.** 1995. Digestive cryptosporidiosis in young children in an urban area in Gabon. Sante **5:**185–188.
39. **Escobedo, A. A., and F. A. Nunez.** 1999. Prevalence of intestinal parasites in Cuban acquired immunodeficiency syndrome (AIDS) patients. Acta Trop. **72:**125–130.
40. **Fayer, R., and B. L. P. Ungar.** 1986. *Cryptosporidium* spp. and cryptosporidiosis. Microbiol. Rev. **50:**458–483.
41. **Fisseha, B., B. Petros, and T. WoldeMichael.** 1998. *Cryptosporidium* and other parasites in Ethiopian AIDS patients with chronic diarrhoea. East Afr. Med. J. **75:**100–101.
42. **Foot, A. B., and A. Oakhill, and M. G. Mott.** 1990. Cryptosporidiosis and acute leukaemia. Arch. Dis. Child. **65:**236–237.
43. **Forbes, A., C. Blanshard, and B. Gazzard.** 1993. Natural history of AIDS related sclerosing cholangitis: a study of 20 cases. Gut **34:**116–121.
44. **Foudraine, N. A., G. J. Weverling, T. van Gool, M. T. Roos, F. de Wolf, P. P. Koopmans, P. J. van den Broek, P. L. Meenhorst, H. van Leeuwen, J. M. Lange, and P. Reiss.** 1998. Improvement of chronic diarrhoea in patients with advanced HIV-1 infection during potent antiretroviral therapy. AIDS **12:**35–41.
45. **Garone, M. A., B. J. Winston, and J. H. Lewis.** 1986. Cryptosporidiosis of the stomach. Am. J. Gastroenterol. **81:**465–470.
46. **Gentile, G., A. Caprioli, G. Donelli, M. Venditti, F. Mandelli, and P. Martino.** 1990. Asymptomatic carriage of *Cryptosporidium* in two patients with leukemia. Am. J. Infect. Control **18:**127–128.
47. **Gentile, G., M. Venditti, A. Micozzi, A. Caprioli, G. Donelli, C. Tirindelli, G. Meloni, W. Arcese, and P. Martino.** 1991. Cryptosporidiosis in patients with hematologic malignancies. Rev. Infect. Dis. **13:**842–846.
48. **Gerber, D. A., M. Green, R. Jaffe, D. Greenberg, G. Mazariegos, and J. Reyes.** 2000. Cryptosporidial infections after solid organ transplantation in children. Pediatr. Transplant. **4:**50–55.
49. **Glaser, C. A., S. Safrin, A. Reingold, and T. B. Newman.** 1998. Association between *Cryptosporidium* infection and animal exposure in HIV-infected individuals. J. Acquired Immune Defic Syndr. **17:**79–82.
50. **Godwin, T. A.** 1991. Cryptosporidiosis in the acquired immunodeficiency syndrome: a study of 15 autopsy cases. Hum. Pathol. **22:**1215–1224.
51. **Gomez Morales, M. A., C. M. Ausiello, A. Guarino, F. Urbani, M. I. Spagnuolo, C. Pignata, and E. Pozio.** 1996. Severe, protracted intestinal cryptosporidiosis associated with interferon gamma deficiency: pediatric

case report. Clin. Infect. Dis. **22:**848–850.

52. **Griffiths, J. K.** 1998. Human cryptosporidiosis: epidemiology, transmission, clinical disease, treatment, and diagnosis. Adv. Parasitol. **40:**37–85.

53. **Guarino, A., A. Castaldo, S. Russo, M. I. Spagnuolo, R. B. Canani, L. Tarallo, L. DiBenedetto, and A. Rubino.** 1997. Enteric cryptosporidiosis in pediatric HIV infection. J. Pediatr. Gastroenterol. Nutr. **25:**182–187.

54. **Harp, J. A., R. Fayer, B. A. Pesch, and G. J. Jackson.** 1996. Effect of pasteurization on infectivity of *Cryptosporidium parvum* oocysts in water and milk. Appl. Environ. Microbiol. **62:**2866–2868.

55. **Hashmey, R., N. H. Smith, S. Cron, E. A. Graviss, C. L. Chappell, and A. C. White, Jr.** 1997. Cryptosporidiosis in Houston, Texas. A report of 95 cases. Medicine **76:**118–139.

56. **Hayward, A. R., J. Levy, F. Facchetti, L. Notarangelo, H. D. Ochs, A. Etzioni, J. Y. Bonnefoy, M. Cosyns, and A. Weinberg.** 1997. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J. Immunol. **158:**977–983.

57. **Hayward, A. R., K. Chmura, and M. Cosyns.** 2000. Interferon-gamma is required for innate immunity to *Cryptosporidium parvum* in mice. J. Infect. Dis. **182:**1001–1004.

58. **Hunter, P. R.** 1997. Water-borne disease: epidemiology and ecology. John Wiley & Sons, Inc., Chichester, United Kingdom.

59. **Iribarren, J. A., A. Castiella, C. Lobo, P. Lopez, M. A. von Wichmann, J. Arrizabalaga, F. J. Rodriguez-Arrondo, and L. F. Alzate.** 1997. AIDS-associated cryptosporidiosis with antral narrowing. A new case. J. Clin. Gastroenterol. **25:**693–694.

60. **Jacyna, M. R., J. Parkin, R. Goldin, and J. H. Baron.** 1990. Protracted enteric cryptosporidial infection in selective immunoglobulin A and *Saccharomyces* opsonin deficiencies. Gut **31:**714–716.

61. **Jaggi, N., S. Rajeshwari, S. K. Mittal, M. D. Mathur, and U. K. Baveja.** 1994. Assessment of the immune and nutritional status of the host in childhood diarrhoea due to cryptosporidium. J. Commun. Dis. **26:**181–185.

62. **Janoff, E. N., P. S. Mead, J. R. Mead, P. Echeverria, L. Bodhidatta, M. Bhaibulaya, C. R. Sterling, and D. N. Taylor.** 1990. Endemic *Cryptosporidium* and *Giardia lamblia* infections in a Thai orphanage. Am. J. Trop. Med. Hyg. **43:**248–256.

63. **Javier Enriquez, F., C. R. Avila, J. Ignacio Santos, J. Tanaka-Kido, O. Vallejo, and C. R. Sterling.** 1997. *Cryptosporidium* infections in Mexican children: clinical, nutritional, enteropathogenic, and diagnostic evaluations. Am. J. Trop. Med. Hyg. **56:**254–257.

64. **Kazlow, P. G., K. Shah, K. J. Benkov, R. Dische, and N. S. LeLeiko.** 1986. Esophageal cryptosporidiosis in a child with acquired immune deficiency syndrome. Gastroenterology **91:**1301–1303.

65. **Kern, W., S. Mayer, P. Kreuzer, and E. Vanek.** 1987. Low prevalence of intestinal cryptosporidiosis among immunocompetent and immunocompromised patients with and without diarrhoea in southern Germany. Infection **15:**440–443.

66. **Kibbler, C. C., A. Smith, S. J. Hamilton-Dutoit, H. Milburn, J. K. Pattinson, and H. G. Prentice.** 1987. Pulmonary cryptosporidiosis occurring in a bone marrow transplant patient. Scand. J. Infect. Dis. **19:**581–584.

67. **Kocoshis, S. A., M. L. Cibull, T. E. Davis, J. T. Hinton, M. Seip, and J. G. Banwell.** 1984. Intestinal and pulmonary cryptosporidiosis in an infant with severe combined immune deficiency. J. Pediatr. Gastroenterol. Nutr. **3:**149–157.

68. **Le Moing, V., F. Bissuel, D. Costagliola, Z. Eid, F. Chapuis, J. M. Molina, D. Salmon-Ceron, P. Brasseur, and C. Leport.** 1998. Decreased prevalence of intestinal cryptosporidiosis in HIV-infected patients concomitant to the widespread use of protease inhibitors. AIDS **12:**1395–1397.

69. **Levy, J., T. Espanol-Boren, C. Thomas, A. Fischer, P. Tovo, P. Bordigoni, I. Resnick, A. Fasth, M. Baer, L. Gomez, E. A. Sanders, M. D. Tabone, D. Plantaz, A. Etzioni, V. Monafo, M. Abinun, L. Hammarstrom, T. Abrabamsen, A. Jones, A. Finn, T. Klemola, E. DeVries, O. Sanal, M. C. Peitsch, and L. D. Notarangelo.** 1997. Clinical spectrum of X-linked hyper-IgM syndrome. J. Pediatr. **131:**47–54.

70. **Lewis, I. J., C. A. Hart, and D. Baxby.** 1985. Diarrhoea due to *Cryptosporidium* in acute lymphoblastic leukemia. Arch. Dis. Child. **60:**60–62.

71. **Lopez-Velez, R., R. Tarazona, A. Garcia Camacho, E. Gomez-Mampaso, A. Guerrero, V. Moreira, and R. Villanueva.** 1995. Intestinal and extraintestinal cryptosporidiosis in AIDS patients. Eur. J. Clin. Microbiol. Infect. Dis. **14:**677–681.

72. **Macfarlane, D. E., and J. Horner-Bryce.** 1987. Cryptosporidiosis in well-nourished and malnourished children. Acta Paediatr. Scand. **76:**474–477.

73. **MacKenzie, W. R., N. J. Hoxie, M. E. Proctor, M. S. Gradus, K. A. Blair, D. E. Peterson, J. J. Kazmierczak, D. G. Addiss, K. R. Fox, J. B. Rose, and J. P. Davis.** 1994. A massive outbreak in Milwaukee of *Cryptosporidium* infection transmitted through the public water supply. N. Engl. J. Med. **331:**161–167.

74. **Maggi, P., A. M. Larocca, M. Quarto, G. Serio, O. Brandonisio, G. Angarano, and G. Pastore.** 2000. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. Eur. J. Clin. Microbiol. Infect. Dis. **19:**213–217.

75. **Manabe, Y. C., D. P. Clark, R. D. Moore, J. A. Lumadue, H. R. Dahlman, P. C. Belitsos, R. E. Chaisson, and C. L. Sears.** 1998 Cryptosporidiosis in

patients with AIDS: correlates of disease and survival. Clin. Infect. Dis. **27:**536–542.

76. **Manivel, C., A. Filipovich, and D. C. Snover.** 1985. Cryptosporidiosis as a cause of diarrhea following bone marrow transplantation. Dis. Colon Rectum **28:**741–742.

77. **Martino, P., G. Gentile, A. Caprioli, L. Baldassarri, G. Donelli, W. Arcese, S. Fenu, A. Micozzi, M. Venditti, and F. Mandelli.** 1988. Hospital-acquired cryptosporidiosis in a bone marrow transplantation unit. J. Infect. Dis. **158:**647–648.

78. **Matos, O., A. Tomas, P. Aguiar, D. Casemore, and F. Antunes.** 1998. Prevalence of cryptosporidiosis in AIDS patients with diarrhoea in Santa Maria Hospital, Lisbon. Folia Parasitol. **45:**163–166.

79. **McDonald, V., and G. J. Bancroft.** 1998. Immunological control of *Cryptosporidium* infection. Chem. Immunol. **70:**103–123.

80. **McGowan, I., A. S. Hawkins, and I. V. Weller.** 1993. The natural history of cryptosporidial diarrhoea in HIV-infected patients. AIDS **7:**349–354.

81. **McLauchlin, J., C. Amar, S. Pedraza-Diaz, and G. L. Nichols.** 2000. Molecular epidemiological analysis of *Cryptosporidium* spp. in the United Kingdom: results of genotyping *Cryptosporidium* spp. in 1,705 fecal samples from humans and 105 fecal samples from livestock animals. J. Clin. Microbiol. **38:**3984–3990.

82. **Mead, J. R., and X. You.** 1998. Susceptibility differences to *Cryptosporidium parvum* infection in two strains of gamma interferon knockout mice. J. Parasitol. **84:**1045–1048.

83. **Meinhardt, P. L., D. P. Casemore, and K. B. Miller.** 1996. Epidemiologic aspects of human cryptosporidiosis and the role of waterborne transmission. Epidemiol. Rev. **18:**118–136.

84. **Meisel, J. L., D. R. Perera, C. Meligro, and C. E. Rubin.** 1976. Overwhelming watery diarrhoea associated with a *Cryptosporidium* in an immunosuppressed patient. Gastroenterology **70:**1156–1160.

85. **Mengesha, B.** 1994. Cryptosporidiosis among medical patients with the acquired immunodeficiency syndrome in Tikur Anbessa Teaching Hospital, Ethiopia. East Afr. Med. J. **71:**376–378.

86. **Menon, B. S., M S. Abdullah, F. Mahamud, and B. Singh.** 1999. Intestinal parasites in Malaysian children with cancer. J. Trop. Pediatr. **45:**241–242.

87. **Miao, Y. M., F. M. Awad-El-Kariem, C. Franzen, D. S. Ellis, A. Muller, H. M. Counihan, P. J. Hayes, and B. G. Gazzard.** 2000. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. J. Acquired Immune Defic. Syndr. **25:**124–129.

88. **Molbak, K., M. Andersen, P. Aaby, N. Hojlyng, M. Jakobsen, M. Sodemann, and A. P. da Silva.** 1997. *Cryptosporidium* infection in infancy as a cause of malnutrition: a community study from Guinea-Bissau, West Africa. Am. J. Clin. Nutr. **65:**149–152.

89. **Morgan, U., R. Weber, L. Xiao, I. Sulaiman, R. C. Thompson, W. Ndiritu, A. Lal, A. Moore, and P. Deplazes.** 2000. Molecular characterization of *Cryptosporidium* isolates obtained from human immunodeficiency virus-infected individuals living in Switzerland, Kenya, and the United States. J. Clin. Microbiol. **38:**1180–1183.

90. **Moolasart, P., B. Eampokalap, M. Ratanasrithong, P. Kanthasing, S. Tansupaswaskul, and C. Tanchanpong.** 1995. Cryptosporidiosis in HIV infected patients in Thailand. Southeast Asian J. Trop. Med. Public Health **26:**335–338.

91. **Moon, A., W. Spivak, and L. J. Brandt.** 1999. *Cryptosporidium*-induced gastric obstruction in a child with congenital HIV infection: case report and review of the literature. J. Pediatr. Gastroenterol. Nutr. **28:**108–111.

92. **Nachbaur, D., G. Kropshofer, H. Feichtinger, F. Allerberger, and D. Niederwieser.** 1997. Cryptosporidiosis after CD34-selected autologous peripheral blood stem cell transplantation (PBSCT). Treatment with paromomycin, azithromycin and recombinant human interleukin-2. Bone Marrow Transplant. **19:**1261–1263.

93. **Navin, T. R., R. Weber, D. J. Vugia, D. Rimland, J. M. Roberts, D. G. Addiss, G. S. Visvesvara, S. P. Wahlquist, S. E. Hogan, L. E. Gallagher, D. D. Juranek, D. A. Schwartz, C. M. Wilcox, J. M. Stewart, S. E. Thompson III, and R. T. Bryan.** 1999. Declining CD4+ T-lymphocyte counts are associated with increased risk of enteric parasitosis and chronic diarrhea: results of a 3-year longitudinal study. J. Acquired Immune Defic. Syndr. **20:**154–159.

94. **Neira, P., M. T. Tardio, M. Carabelli, and L. Villalon.** 1989. Cryptosporidiosis in the V Region Chile. III. Study of malnourished patients, 1985–1987. Bol. Chil. Parasitol. **44:**34–36.

95. **Nime, F. A., J. D. Burek, D. L. Page, M. A. Holscher, and J. H. Yardley.** 1976. Acute enterocolitis in a human being infected with the protozoan *Cryptosporidium*. Gastroenterology **70:**592–598.

96. **Oberhuber, G., E. Lauer, M. Stolte, and F. Borchard.** 1991. Cryptosporidiosis of the appendix vermiformis: a case report. Z. Gastroenterol. **29:**606–608.

97. **Ok, U. Z., M. Cirit, A. Uner, E. Ok, F. Akcicek, A. Basci, and M. A. Ozcel.** 1997. Cryptosporidiosis and blastocystosis in renal transplant recipients. Nephron **75:**171–174.

98. **Pedersen, C., S. Danner, A. Lazzarin, M. P. Glauser, R. Weber, C. Katlama, S. E. Barton, and J. D. Lundgren.** 1996. Epidemiology of cryptosporidiosis among European AIDS patients. Genitourin. Med. **72:**128–131.

99. **Pedraza-Díaz, S., C. Amar, A. M. Iversen, P. J. Stanley, and J. McLauchlin.** 2001. Unusual *Cryptosporidium* species recovered from human faeces: first description of *Cryptosporidium felis* and *Cryptosporidium* 'dog type' from patients in England. J. Med. Microbiol. **50:**293–296.

100. **Pedraza-Díaz, S., C. F. L. Amar, J. McLauchlin, G. L. Nichols, K. M. Cotton, P. Godwin, A. M. Iversen, L. Milne, J. R. Mulla, K. Nye, H. Panigrahi, S. R. Venn, R. Wiggins, M. Williams, and E. R. Youngs.** 2001. *Cryptosporidium meleagridis* from humans: molecular analysis and description of affected patients. J. Infect. **42:**243–250.

101. **Pieniazek, N. J., F. J. Bornay-Llinares, S. B. Slemenda, A. J. da Silva, I. N. Moura, M. J. Arrowood, O. Ditrich, and D. G. Addiss.** 1999. New *Cryptosporidium* genotypes in HIV-infected persons. Emerg. Infect. Dis. **5:**444–449.

102. **Ravn, P., J. D. Lundgren, P. Kjaeldgaard, W. Holten-Anderson, N. Hojlyng, J. O. Nielsen, and J. Gaub.** 1991. Nosocomial outbreak of cryptosporidiosis in AIDS patients. Br. Med. J. **302:**277–280.

103. **Roncoroni, A. J., M. A. Gomez, J. Mera, P. Cagnoni, and M. D. Michel.** 1989. *Cryptosporidium* infection in renal transplant patients. J. Infect. Dis. **160:**559.

104. **Rossi, P., F. Rivasi, M. Codeluppi, A. Catania, A. Tamburrini, E. Righi, and E. Pozio.** 1998. Gastric involvement in AIDS associated cryptosporidiosis. Gut **43:**476–477.

105. **Sallon, S., R. J. Deckelbaum, I. I. Schmid, S. Harlap, M. Baras, and D. T. Spira.** 1988. Cryptosporidium, malnutrition, and chronic diarrhea in children. Am. J. Dis. Child. **142:**312–315.

106. **Samson, V. E., and W. R. Brown.** 1996. Pneumatosis cystoides intestinalis in AIDS-associated cryptosporidiosis. More than an incidental finding? J. Clin Gastroenterol. **22:**311–312.

107. **Sarabia-Arce, S., E. Salazar-Lindo, R. H. Gilman, J. Naranjo, and E. Miranda.** 1990. Case-control study of *Cryptosporidium parvum* infection in Peruvian children hospitalized for diarrhea: possible association with malnutrition and nosocomial infection. Pediatr. Infect. Dis. J. **9:**627–631.

108. **Sauda, F. C., L. A. Zamarioli, W. Ebner Filho, and L. de B. Mello.** 1993. Prevalence of *Cryptosporidium* spp. and *Isospora belli* among AIDS patients attending Santos Reference Center for AIDS, Sao Paulo, Brazil. J. Parasitol. **79:**454–456.

109. **Sidhu, S., S. Flamm, and S. Chopra.** 1994. Pneumatosis cystoides intestinalis: an incidental finding in a patient with AIDS and cryptosporidial diarrhea. Am. J. Gastroenterol. **89:**1578–1579.

110. **Smart, B. A., and H. D. Ochs.** 1997. The molecular basis and treatment of primary immunodeficiency disorders. Curr. Opin. Pediatr. **9:**570–576.

111. **Sorvillo, F., G. Beall, P. A. Turner, V. L. Beer, A. A. Kovacs, P. Kraus, D. Masters, and P. R. Kerndt.** 1998. Seasonality and factors associated with cryptosporidiosis among individuals with HIV infection. Epidemiol Infect. **121:**197–204.

112. **Sorvillo, F. J., L. E. Lieb, P. R. Kerndt, and L. R. Ash.** 1994. Epidemiology of cryptosporidiosis among persons with acquired immunodeficiency syndrome in Los Angeles County. Am. J. Trop. Med. Hyg. **51:**326–331.

113. **Sreedharan, A., R. S. Jayshree, and H. Sridhar.** 1996. Cryptosporidiosis among cancer patients: an observation. J. Diarrhoeal Dis. Res. **14:**211–213.

114. **Stine, K. C., J. S. Harris, N. J. Lindsey, and C. T. Cho.** 1985. Spontaneous remission of cryptosporidiosis in a child with acute lymphocytic leukemia. Clin. Pediatr. **24:**722–724.

115. **Taghi-Kilani, R., L. Sekla, and K. T. Hayglass.** 1990. The role of humoral immunity in *Cryptosporidium* spp. infection. Studies with B cell-depleted mice. J. Immunol. **145:**1571–1576.

116. **Tanyuksel, M., H. Gun, and L. Doganci.** 1995. Prevalence of *Cryptosporidium* spp. in patients with neoplasia and diarrhea. Scand. J. Infect. Dis. **27:**69–70.

117. **Theodos, C. M.** 1998 Innate and cell-mediated immune responses to *Cryptosporidium parvum*. Adv. Parasitol. **40:**87–119.

118. **Theodos, C. M., K. L. Sullivan, J. K. Griffiths, and S. Tzipori.** 1997. Profiles of healing and nonhealing *Cryptosporidium parvum* infection in C57BL/6 mice with functional B and T lymphocytes: the extent of gamma interferon modulation determines the outcome of infection. Infect. Immun. **65:**4761–4769.

119. **Travis, W. D., K. Schmidt, J. D. MacLowry, H. Masur, K. S. Condron, and A. T. Fojo.** 1990 Respiratory cryptosporidiosis in a patient with malignant lymphoma. Report of a case and review of the literature. Arch. Pathol. Lab. Med. **114:**519–522.

120. **Trevino-Perez, S., G. Luna-Castanos, A. Matilla-Matilla, and L. Nieto-Cisneros.** 1995. Chronic diarrhea and *Cryptosporidium* in diabetic patients with normal lymphocyte subpopulation. 2 case reports. Gaceta Med. Mex. **131:**219–222.

121. **Tsaihong, J. C., P. Guiguli, M. Y. Liou, and P. Ma.** 1990. Cryptosporidiosis in AIDS and non-AIDS patients. Chin. J. Microbiol. Immunol. **23:**155–161.

122. **Tzipori, S.** 1998. Cryptosporidiosis: laboratory investigations and chemotherapy. Adv. Parasitol. **40:**187–221.

123. **Urban, J. F. J., R. Fayer, S. J. Chen, W. C. Gause, M. K. Gately, and F. D. Finkelman.** 1996. IL-12 protects immunocompetent and immunodeficient neonatal mice against infection with *Cryptosporidium parvum*. J. Immunol. **156:**263–268.

124. **Uga, S., N. Kunaruk, S. K. Rai, and M. Watanabe.** 1998. *Cryptosporidium* infection in HIV-seropositive and seronegative populations in southern Thailand. Southeast Asian J. Trop. Med. Public Health **29:**100–104.

125. **Vajro, P., L. di Martino, S. Scotti, C. Barbati, A. Fontanella, and M. Pettoello Mantovani.** 1991. Intestinal *Cryptosporidium* carriage in two liver-transplanted children. J. Pediatr. Gastroenterol. Nutr. **12:**139.

126. **Vakil, N. B., S. M. Schwartz, B. P. Buggy, C. F. Brummitt, M. Kherellah, D. M. Letzer, I. H. Gilson, and P. G. Jones.** 1996. Biliary cryptosporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. N. Engl. J. Med. **334:**19–23.

127. **Ventura, G., R. Cauda, L. M. Larocca, M. E. Riccioni, M. Tumbarello, and M. B. Lucia.** 1997. Gastric cryptosporidiosis complicating HIV infection: case report and review of the literature. Eur. J. Gastroenterol. Hepatol. **9:**307–310.

128. **Wells, G. M., A. Gajjar, T. A. Pearson, K. L. Hale, and J. L. Shenep.** 1998. Brief report. Pulmonary cryptosporidiosis and *Cryptococcus albidus* fungemia in a child with acute lymphocytic leukemia. Med. Pediatr. Oncol. **31:**544–546.

129. **White, A. C., P. Robinson, P. C. Okhuysen, D. E. Lewis, I. Shahab, S. Lahoti, H. L. DuPont, and C. L. Chappell.** 2000. Interferon-gamma expression in jejunal biopsies in experimental human cryptosporidiosis correlates with prior sensitization and control of oocyst excretion. J. Infect. Dis. **181:**701–709.

130. **Widmer, G., S. Tzipori, C. J. Fichtenbaum, and J. K. Griffiths.** 1998. Genotypic and phenotypic characterization of *Cryptosporidium parvum* isolates from people with AIDS. J. Infect. Dis. **178:**834–840.

131. **Xiao, L., U. M. Morgan, R. Fayer, R. C. A. Thompson, and A. A. Lal.** 2000. *Cryptosporidium* systematics and implications for public health. Parasitol. Today **16:**287–292.

132. **Xiao, L., C. Bern, J. Limor, I. Sulaiman, J. Roberts, W. Checkley, L. Cabrera, R. H. Gilman, and A. A. Lal.** 2001. Identification of 5 types of *Cryptosporidium* parasites in children in Lima, Peru. J. Infect. Dis. **183:**492–497.